

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

THURSDAY 25 NOV 2004
[Signature]

To:

Davies Collison Cave
Level 15
1 Nicholson Street
MELBOURNE VIC 3000

PCT

NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY EXAMINATION
REPORT

(PCT Rule 71.1)

Date of mailing
day/month/year

24 NOV 2004

Applicant's or agent's file reference
12301370/EJH/ar

IMPORTANT NOTIFICATION

International Application No.
PCT/AU2003/001006

International Filing Date

8 August 2003

Priority Date

9 August 2002

Applicant

MELBOURNE HEALTH et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

Name and mailing address of the IPEA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaaustralia.gov.au
Facsimile No. (02) 6285 3929

Authorized officer

TERRY MOORE

Telephone No. (02) 6283 2632

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PATENT COOPERATION TREATY
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 12301370/EJH/ar	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/AU2003/001006	International Filing Date (<i>day/month/year</i>) 8 August 2003	Priority Date (<i>day/month/year</i>) 9 August 2002
International Patent Classification (IPC) or national classification and IPC Int. Cl. 7 C12N 15/12, C07K 14/435, 16/18		
Applicant MELBOURNE HEALTH et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.																
2. This REPORT consists of a total of 7 sheets, including this cover sheet. <input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 4 sheet(s).																
3. This report contains indications relating to the following items: <table style="margin-left: 20px;"> <tr><td>I</td><td><input checked="" type="checkbox"/> Basis of the report</td></tr> <tr><td>II</td><td><input checked="" type="checkbox"/> Priority</td></tr> <tr><td>III</td><td><input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td></tr> <tr><td>IV</td><td><input type="checkbox"/> Lack of unity of invention</td></tr> <tr><td>V</td><td><input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td></tr> <tr><td>VI</td><td><input checked="" type="checkbox"/> Certain documents cited</td></tr> <tr><td>VII</td><td><input type="checkbox"/> Certain defects in the international application</td></tr> <tr><td>VIII</td><td><input type="checkbox"/> Certain observations on the international application</td></tr> </table>	I	<input checked="" type="checkbox"/> Basis of the report	II	<input checked="" type="checkbox"/> Priority	III	<input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	IV	<input type="checkbox"/> Lack of unity of invention	V	<input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	VI	<input checked="" type="checkbox"/> Certain documents cited	VII	<input type="checkbox"/> Certain defects in the international application	VIII	<input type="checkbox"/> Certain observations on the international application
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VIII	<input type="checkbox"/> Certain observations on the international application															

Date of submission of the demand 20 November 2003	Date of completion of the report 19 November 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer TERRY MOORE Telephone No. (02) 6283 2632

I. Basis of the report

1. With regard to the elements of the international application:*

the international application as originally filed.

the description, pages **1-81 and 86**, as originally filed,
pages , filed with the demand,
pages , received on with the letter of

the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **82-85**, received on **16 November 2004** with the letter of **16 November 2004**

the drawings, pages **1/9-9/9**, as originally filed,
pages , filed with the demand,
pages , received on with the letter of

the sequence listing part of the description:
pages **1-84**, as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language which is:

the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

the language of publication of the international application (under Rule 48.3(b)).

the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

contained in the international application in written form.

filed together with the international application in computer readable form

furnished subsequently to this Authority in written form

furnished subsequently to this Authority in computer readable form.

The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. The amendments have resulted in the cancellation of:

the description, pages

the claims, Nos.

the drawings, sheets/fig.

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report

II. Priority

1. This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1).

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

It appears some of the claims of the application may not be entitled to the claimed priority date as the information was disclosed by some of the inventors of the instant application in an earlier document, Wilanowski T *et al.* (June 2002) Mech Dev. 114(1-2): 37-50 (D1) more than 12 months before the filing date of the Application. Mammalian MGR and BOM sequences are disclosed in this document. The only sequences that appear to be entitled to the claimed priority date are those related to SOM.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 11 and 13-15	YES
	Claims 1-10 and 12	NO
Inventive step (IS)	Claims 13	YES
	Claims 1-12, 14 and 15	NO
Industrial applicability (IA)	Claims 1-15	YES
	Claims	NO

2. Citations and explanations (Rule 70.7)

The following citations from the International Search Report are referred to in this report:

D1 = Wilanowski T *et al.* (June 2002) *Mech Dev.* 114(1-2): 37-50.

D2 = Ting SB *et al.* (2003) *Biochem J.* 370(Pt 3): 953-62.

D3 = Strausberg R L *et al.* (2002) *Proc. Natl. Acad. Sci USA* 99(26): 16899-16903.

D4 = WO 2003/006618.

D5 = WO 2002/070539.

D6 = WO 2002/071928.

D7 = WO 2002/030268.

D8 = EP 1074617.

D9 = DGENE Abstract Accession No. AAG67096, CN 1303939.

D10 = WO 2000/058473.

D11 = WO 2001/075067.

D12 = Huang N & Miller W L (2000) *J Biol. Chem.* 275(4): 2852-2858.

The invention appears to reside in the identification of mammalian homologues to the *drosophila* *grainyhead* transcription factor, specifically MGR, BOM and SOM transcription factors as identified in SEQ ID NOS: 1-16.

As discussed in section II(3), D1, published one month before the earliest priority date of the instant application, appears to invalidate the priority claim for the invention relating to MGR and BOM sequences. Given this, documents D2-D6, although published after the priority date of the present application, appear to be represent prior art with respect to claims relating to MGR and BOM.

Furthermore, D4-D6 are patent documents with earlier priority dates than the present application. Thus even if the priority date for MGR and BOM can be established as the date of filing of the basic application, D4-D6 will still be relevant in National phase examination in some states, such as Australia.

Continued in supplemental box,

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 2003/006618	23 January 2003	10 July 2002	12 July 2001
WO 2002/070539	12 September 2002	5 March 2002	5 March 2001
WO 2002/071928	19 September 2002	14 March 2002	14 March 2001

SEQ ID NO: 30 of WO 2003/006618 (D4) is 99% and 91% identical to SEQ ID NOs: 8 and 16 of the present invention respectively. This document was published after the claimed priority date of the present invention. However, this document has an earlier priority date than the present application and may be relevant to claims 1-10 and 12 in National phase examination in some states, such as Australia.

SEQ ID NO: 1342 of WO 2002/070539 (D5) is 100% and 75% identical to SEQ ID NO: 6 and 14 of the present invention respectively. SEQ ID NO: 91 of WO 2002/071928 (D6) is 99% and 94% identical to SEQ ID NO: 6 and 14 of the present invention respectively. These documents are published after the priority date of the present application. However, the priority date for this application has been found invalid (see box II above). Therefore these two documents are relevant for determining novelty and inventive step (see box V below for more details) of claims relating to MGR and BOM.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

Supplemental Box I

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V2**NOVELTY AND INVENTIVE STEP**

Firstly, the applicant has considered that the five documents cited that are published prior to the international filing date but later than the priority date claimed need not be further considered. The applicant is directed to box II, which questions the priority claim for the sequences. The only sequences that appear to be entitled to the claimed priority date are those related to SOM.

D1 discloses further characterisation of BOM and MGR sequences and the identification of an additional family member, Sister of grainyhead (SOM) (see page 44 left column, last paragraph - right column first paragraph and figure 9), which appears to represent the applicant's SOM sequence.

As such the citation teaches toward the SOM nucleic acids and peptides of claims 1-6 and the animal model and assessment system of claims 14 and 15, thereby depriving these claims of an inventive step.

In addition the citation also deprives claim 11 of an inventive step. Disclosure of MGR and BOM, their characteristics and the wider family provides both the information and the incentive to apply the standard method of database analysis to identify further members of the family and to characterise their expression patterns are recited in claim 11.

D2 discloses the identification and characterisation of human Sister of mammalian grainyhead (SOM) and compares this sequence to MGR, BOM and GRH sequences. Although this document was published after the claimed priority date, the priority date for MGR, BOM and GRH has been found invalid (see Box II above). Therefore claim 11 lacks an inventive step with respect to the use of MGR and BOM sequences to identify further members of *grainyhead* family. It is standard practice in the art to use sequence information relating to a protein of interest to identify further members of that family and to then characterise their expression patterns.

Claims to SOM may have a valid priority claim, consequently D2 does not appear to impact on the novelty and inventive step of claims restricted to SOM.

D3 discloses the identification and sequencing of multiple cDNA clones containing complete ORFs from human and mouse genes. Mouse grainyhead-like mRNA and human SOM grainyhead mRNA were identified. These sequences are 100% identical to parts of the mouse MGR, mouse BOM and human SOM sequences identified in the present application. This document was published after the claimed priority date. However, the priority date has been found invalid (see Box II above). Therefore, for the reasons discussed above, claim 11 lacks an inventive step in light of D3.

D4 discloses the isolation of nucleic acid associated polypeptide sequences and methods of using these polypeptides, for example in treating disease. The polypeptides may be transcription factors. SEQ ID NO: 30 is 98.7% and 91.4% identical to SEQ ID NO: 8 and SEQ ID NO: 16 of the present application (SOM sequences). This document was published after the priority date of the present application. The claims to SOM appear to have a valid priority claim. Thus, the claims are novel but this document may be relevant in National phase examination in some States.

D5 discloses nucleic acid and polypeptide sequences from the human genome and methods of treatment using these sequences to treat physiological and genetic disorders. SEQ ID NO: 1342 is 100% and 74.7% identical to SEQ ID NO: 6 and SEQ ID NO: 14 respectively (BOM). The corresponding nucleotide sequence is SEQ ID NO: 394 (see page 998). This document was published after the priority date of the present application. However, as the priority date is in question the document is relevant to the novelty and inventive step of claims 7-10 and 12.

Continued in supplemental box II.

Supplemental Box II

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Supplemental box I

D6 discloses nucleic acid molecules and proteins associated with ovarian cancer and methods of treatment comprising use of these sequences. SEQ ID NO: 91 is 99.4% and 94.1% identical to BOM SEQ ID NO: 6 and SEQ ID NO: 14 respectively. Due to the high degree of homology these proteins are expected to inherently have transcription factor activity. This document was published after the priority date of the present application. However, as the priority date is in question the document is relevant to the novelty and inventive step of claims 7-10 and 12.

D7 discloses genes whose expression is altered in prostate cancer and methods of treatment based on the use of these sequences. SEQ ID NO: 2 is 99.4% and 94.1% identical to BOM SEQ ID NO: 6 and SEQ ID NO: 14 respectively. Due to the high degree of homology these proteins are expected to inherently have transcription factor activity. As such, the citation is relevant to the novelty and inventive step of claims 7-10 and 12.

D8 discloses multiple human cDNA sequences and their protein sequences and the use of these sequences to identify and characterise further related sequences. SEQ ID NO: 18202 is 99.4% and 94.1% identical to BOM SEQ ID NO: 6 and SEQ ID NO: 14 respectively. Due to the high degree of homology these proteins are expected to inherently have transcription factor activity. As such the citation deprives claim 11 of an inventive step. It is standard practice in the art to use sequence information relating to a protein of interest to identify further members of that family and to then characterise their expression patterns.

D9 discloses a polypeptide transcription factor 43 and the nucleotide sequence that encodes the protein. It also discloses use of the peptide to treat diseases associated with physiological or genetic factors. The protein sequence is 99.4%, 94.9% and 91% identical to SEQ ID NO: 2, SEQ ID NO: 4 and both SEQ ID NO: 10 and 12 respectively. As such the citation deprives claims 7-10 and 12 of novelty and an inventive step.

D10 discloses nucleotide sequences that encode ORFs coding for polypeptides and use of these sequences to treat disease. SEQ ID NO: 3956 (page 3116) is 90.2 %, 96% and 93.1% identical to SEQ ID NO: 2, SEQ ID NO: 4 and both SEQ ID NO: 10 and 12 respectively. Therefore, for the reasons discussed above, claims 7-10 and 12 lack novelty and an inventive step.

D11 discloses nucleic acid and polypeptide molecules from the human genome and methods of treatment using these sequences. SEQ ID NO: 42303 is 100% and 96.6% identical to SOM SEQ ID NO: 8 and SEQ ID NO: 16 respectively. The sequences inherently encode a transcription factor due to the high degree of homology. Therefore claims 1-10 and 12 lack novelty and an inventive step and claims 11, 14 and 15 an inventive step in light of D11.

D12 discloses the LBP-32 protein and nucleic acid sequences. The LBP-32 protein has subsequently been determined to be identical to human MGR transcription factor. The sequence is 100% identical to SEQ ID NO: 4, therefore, for the reasons discussed above claim 11 lacks an inventive step in light of D12.

CLAIMS

1. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a mammalian transcription factor comprising an amino acid sequence selected from SEQ ID NO:8 (human SOM), SEQ ID NO:16 (murine SOM) and an amino acid sequence having at least 75% identity to SEQ ID NO:8 or SEQ ID NO:16 after optimal alignment.
2. The isolated nucleic acid molecule of claim 1 wherein the mammalian transcription factor is encoded by a nucleotide sequence having at least 75% identity after optimal alignment to one or more of SEQ ID NO:7 (human *som*) or SEQ ID NO:15 (murine *som*) or a nucleotide sequence capable of hybridizing to SEQ ID NO:7 or 15 or a complementary form thereof under stringency conditions.
3. The isolated nucleic acid molecule of claim 1 or 2 encoding a polypeptide comprising an amino acid sequence selected from SEQ ID NO:8 and SEQ ID NO:16.
4. The isolated nucleic acid molecule of claim 1 comprising a nucleotide sequence selected from SEQ ID NO:7 and SEQ ID NO:15.
5. An isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO: 7.
6. An isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO: 15.

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7. Use of an isolated nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a mammalian homolog of *Drosophila grh* wherein the nucleic acid molecule encodes a transcription factor selected from human SEQ ID NO: 2 (MGR p49), SEQ ID NO: 4 (human MGR p70), SEQ ID NO: 6 (human BOM), SEQ ID NO: 7 (human SOM), SEQ ID NO: 10 (murine MGR p61), SEQ ID NO: 12 (murine MGR p70), SEQ ID NO: 14 (murine BOM) and SEQ ID NO: 16 (murine SOM) or transcription factor having at least 65% identity to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 or SEQ ID NO:16 after optimal alignment in the manufacture of a medicament for the treatment of spinabifida or other physiological or genetic disorder.
8. Use of claim 7 wherein the mammalian homolog comprises a nucleotide sequence having at least 75% identity after optimal alignment to one or more of SEQ ID NO: 17, SEQ ID NO: 34, SEQ ID NO: 36 and SEQ ID NO: 38 or comprises a nucleotide sequence capable of hybridizing to SEQ ID NO: 17, SEQ ID NO: 34, SEQ ID NO: 36 and/or SEQ ID NO: 38 or a complementary form thereof under stringency conditions.
9. Use of claim 7 wherein the nucleic acid molecule comprises a sequence of nucleotides encoding a polypeptide having transcription factor activity and comprising an amino acid sequence selected from SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 and SEQ ID NO:16.
10. Use of claim 7 wherein the nucleic acid molecule comprises a nucleotide sequence selected from SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13 and SEQ ID NO:15.

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11. A method of identifying a nucleotide sequence likely to encode an M-GRH transcription factor, said method comprising interrogating a mammalian genome database conceptually translated into different reading frames with an amino acid sequence defining *Drosophila GRH* or any one of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 and SEQ ID NO:16 and identifying a nucleotide sequence corresponding to an amino acid sequence having at least about 70% similarity to *Drosophila GRH* or to any one of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 and SEQ ID NO:16 and then determining that the nucleotide sequence exhibits a restricted pattern of expression.
12. Use of an isolated mammalian transcription factor which is a homolog of *Drosophila* grainyhead (GRH) selected from human SEQ ID NO: 2 (MGR p49), SEQ ID NO: 4 (human MGR p70), SEQ ID NO: 6 (human BOM), SEQ ID NO: 8 (human SOM), SEQ ID NO: 10 (murine MGR p61), SEQ ID NO: 12 (murine MGR p70), SEQ ID NO: 14 (murine BOM) and SEQ ID NO: 16 (murine SOM) and a molecule having at least 75% identity to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 or SEQ ID NO:16 after optimal alignment in the manufacture of a medicament for the treatment of spinabifida or other physiological or genetic disorder.
13. A method for detecting an embryo with a propensity to develop spinabifida said method comprising contacting said embryo or a cell therefor with agents capable of detecting the level of expression of a transcription factor selected from human SEQ ID NO: 2 (MGR p49), SEQ ID NO: 4 (human MGR p70), SEQ ID NO: 6 (human BOM), SEQ ID NO: 8 (human SOM), SEQ ID NO: 10 (murine MGR p61), SEQ ID NO: 12 (murine MGR p70), SEQ ID NO: 14 (murine BOM) and SEQ ID NO: 16 (murine SOM) and a molecule having at least 75% identity to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14 or SEQ ID NO:16 after optimal alignment.

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14. An animal model comprising a genetically modified animal comprising a nucleotide insertion, deletion, addition and/or substitution in a nucleic acid molecule comprising a nucleotide sequence having at least 75% identity after optimal alignment to one or more of SEQ ID NO:7 (human *som*) or SEQ ID NO:15 (murine *som*) or a nucleotide sequence capable of hybridizing to SEQ ID NO:7 or 15 or a complementary form thereof under stringency conditions of claim 2.
15. A medical assessment system comprising the animal model of claim 14.

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